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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/698,259	10/31/2003	Beth P. Nguyen	PROTEO.P08CI	7361

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EXAMINER	
KOLKER, DANIEL E	

ART UNIT	PAPER NUMBER
1649	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/698,259	NGUYEN ET AL.	
	Examiner	Art Unit	
	DANIEL KOLKER	1649	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 October 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-8,10 and 33-35* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-8,10 and 33-35* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. The remarks and amendments filed 23 October 2008 have been entered. Claims 1 – 8, 10, and 33 – 35 are pending and under examination.

Continued Examination Under 37 CFR 1.114

2. A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 23 October 2008 has been entered.

Priority

3. The effective filing date of claims 1 – 8 and 10 is 1 November 2002; the effective filing date for claims 33 – 35 is 31 October 2003 for the reasons set forth in the office action mailed 21 December 2007. Applicant did not traverse the examiner's determination that these are the appropriate effective filing dates.

Double Patenting

4. The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. A nonstatutory obviousness-type double patenting rejection is appropriate where the conflicting claims are not identical, but at least one examined application claim is not patentably distinct from the reference claim(s) because the examined application claim is either anticipated by, or would have been obvious over, the reference claim(s). See, e.g., *In re Berg*, 140 F.3d 1428, 46 USPQ2d 1226 (Fed. Cir. 1998); *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970); and *In re Thorington*, 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) or 1.321(d) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting

ground provided the conflicting application or patent either is shown to be commonly owned with this application, or claims an invention made as a result of activities undertaken within the scope of a joint research agreement.

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 1 – 8, 10, and 33 – 35 stand rejected on the ground of nonstatutory obviousness-type double patenting as being unpatentable over claims 1 – 10 of U.S. Patent No. 7,148,001. Although the conflicting claims are not identical, they are not patentably distinct from each other because in each case the claims are drawn to methods comprising forming amyloid plaques, comprising co-incubation of Aβ 1-40 with a glycosaminoglycan; the claims differ only in that the present claims require that GAG be immobilized, which is not explicitly recited in the claims of the '001 patent. In the previous office action, the examiner indicated that this minor difference would have been obvious to one of ordinary skill in the art. Applicant did not traverse the examiner's determination that such a difference would have been obvious. Rather applicant indicated a terminal disclaimer will be filed in the future. As no such disclaimer has yet been filed, the rejection stands.

Claim Rejections - 35 USC § 103

5. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1 – 7 and 33 – 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Castillo 1997 (Journal of Neurochemistry 69:2452-2465) in view of Hornbeck 1991 (Current Protocols in Molecular Biology 11.2.1 – 11.2.22), Grainger (U.S. Patent 6,395,494), and Snow 1994 (Neuron 12:219-234, reference A on IDS filed 21 March 2007).

Castillo teaches methods of quantitating the amount of Aβ bound to perlecan, which is a sulfated glycosaminoglycan. The methods involve immobilizing the SGAG on a selected medium, and adding the Aβ which is known to be fibrillar, to the medium. See Castillo, p. 2454, first paragraph. The assay is akin to an ELISA, although it relies upon the interaction between Aβ and perlecan rather than between an antibody and it antigen. As set forth previously, the Aβ and SGAG are in a 1:1 ratio, recited in claim 5 and encompassed by claims 1 - 4. Castillo teaches that the medium is a titer well plate (p. 2454, first paragraph), as recited in claim 6. Finally, Castillo teaches that perlecan is a heparan sulfate (see abstract, first sentence; see also p. 2453 first paragraph), as recited in claim 7. However Castillo does not explicitly teach the step of air-drying the SGAG on the medium, as recited in claim 1. Additionally Castillo does not explicitly teach the steps of staining with Congo Red and viewing under polarized light and does not explicitly teach that Maltese-cross patterns are formed, as recited in claim 1.

Hornbeck teaches that the ELISA is a well-known assay format useful to detect the amount of a specific reagent in a solution. Hornbeck teaches that the method relies on antibody-antigen interaction, wherein an antibody specifically binds to its cognate antigen. Hornbeck teaches several types of ELISA, and specifically teaches that in all types of the assay the first reagent (usually an antigen) is adsorbed onto a solid surface, and then solutions containing the compound to be analyzed are usually added. Finally, a detecting step is performed to determine how much of the compound is present and bound to the adsorbed antigen. See pp. 11.2.1 – 11.2.2. Hornbeck teaches that the step of immobilizing the first product on the substrate can be performed at 4°C or at 37°C, and can be done between 2 hours to "overnight" (i.e., about 16 hours); see p. 11.2.4 first paragraph. However Hornbeck does not explicitly teach drying the first product on to the substrate as part of the immobilizing process, and does not teach either Aβ or SGAG, and does not teach Congo Red staining or polarized light, as recited in claim 1.

Grainger teaches an ELISA method to detect the amount of specific TGF-β in solution. The assay is described beginning at column 48 line 42. The assay involves the step of coating the microtiter wells with the first antigen (in this case, an antibody), and allowing the antigen

(here, an antibody) to dry by evaporation at room temperature, which Grainger teaches is about 12 hours (see column 48 lines 45 - 48). This is on point to the limitation "allowing SGAG to air dry on the selected medium" recited in claim 1. Grainger teaches that following subsequent washing steps, the solution containing the substance to be analyzed (here, test samples or stock TGF-β solution) is added, and then detected with detection antibodies, horseradish peroxidase, and a chromogen (see column 49 lines 49 – 67). While Grainger does not specifically teach the temperature at which the assay was performed, it is reasonable that it was performed at room temperature, which is about 25 °C and therefore on point to claim 33. However Grainger does not teach either Aβ or SGAG, and does not teach Congo Red staining or polarized light, as recited in claim 1.

Snow teaches that when perlecan, which is an SGAG, is administered to rats that have received Aβ 1-40, the degree of fibril formation is increased as compared to those who have received only Aβ; see p. 223 second column last complete paragraph - p. 224 line 2 of the text. Snow also teaches that the fibrils can be stained with Congo Red, and following such staining the fibrils form Maltese Cross patterns when viewed under polarized light. See p. 223 last complete paragraph, which indicates that the Maltese cross pattern is present following Congo Red staining and p. 231 paragraph spanning the two columns which indicates that polarized light is used to view Congo Red-stained slides. This is on point to the newly-added limitations to claim 1, directed to the steps of Congo Red staining and viewing with polarized light. However while Snow teaches that perlecan increases the amount of Aβ1-40 fibril formation and Maltese Cross induction *in vivo*, the reference does not explicitly teach immobilizing the SGAG on a selected medium and allowing it to air-dry, as required by claim 1.

It would have been obvious to one of ordinary skill in the art to modify the method of Castillo to include the step of allowing the first product to air dry, as taught by Grainger, with a reasonable expectation of success. The motivation to do so would be to develop an accurate and reliable ELISA-type assay for quantitating the amount of Aβ in a sample. This motivation comes directly from the references themselves, as Castillo teaches an assay for detection, Hornbeck teaches that the assay shares many of the same steps and goals as the well-known ELISA family of assays, and Grainger teaches a specific ELISA that includes the step of allowing the first product to dry completely. Allowing the product to air dry would be advantageous, as it would assure that all the first reagent (in this case, the SGAG perlecan) would be immobilized onto the substrate. The skilled artisan would have been motivated to take

this step, as Castillo teaches that only about 20% of perlecan is immobilized on a microtiter well. Thus by performing this step, the artisan would reasonably expect to have more perlecan immobilized, thereby allowing for a greater range of detection in the assay. In the remarks filed 23 October 2008, applicant argued that there may be drawbacks in performing this additional step. Applicant states that there would be no reason to modify the assay of Castillo by air-drying the SGAG and presents exhibits which indicate that air-drying can change the properties of a protein or an assay in some instances. The examiner has carefully considered the evidence, but it does not contradict the guidance provided by Grainger, who teaches that air-drying is a standard step in developing these assays. There is no reason to believe that the possible problems mentioned in the references cited by applicant would apply to all molecules when air-dried, and since Grainger teaches that reagents should be air-dried, the rejection stands. Applicant also states (remarks, paragraph spanning pp. 8 – 9) that since perlecan is not an antibody but a glycosaminoglycan, unpredictable consequences may result. There is no evidence of record indicating that anything unpredictable would happen to perlecan in particular or glycosaminoglycans in general upon air-drying.

Additionally, inclusion of the steps of staining with Congo Red and viewing under polarized light would have been obvious, given the teachings of Snow 1994. Snow indicates that when Aβ fibrils form, the Maltese Cross pattern is present following Congo Red staining and polarized light microscopy. So including these particular steps would have been obvious, as doing so would allow the artisan to confirm that fibrils had formed, and that the time of incubation was sufficient.

Note that claims 34 and 35 in this rejection as well. As set forth in the previous office actions, optimizing the time and temperature of the assay are within the skill of the artisan. Applicant did not traverse the examiner's determination that the specific limitations of claims 34 – 35 are obvious over the prior art references cited previously. Additionally, given that the reference by Snow is on point to *in vivo* formation of fibrils in mammals, which happens at 37 °C as recited in claim 34, that reference gives guidance to selecting this particular temperature.

6. Claims 1 – 8 and 33 – 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Castillo in view of Hornbeck, Grainger, and Snow as applied to claims 1 – 7 and 33 – 35 above, and further in view of Cross (1989. Journal of Tissue Culture Methods 12:57-59, of record).

This rejection stands for the reasons explained above and previously made of record. The reasons why claims 1 – 7 and 33 – 35 are obvious over Castillo in view of Hornbeck Grainger and Snow are set forth above. However none of the references teaches 96-well PTFE fluoropolymer partitioned slides as encompassed by claim 8.

As set forth previously, Cross teaches a 96-well Teflon (PTFE fluoropolymer)-coated partitioned block, which could reasonably be called a "slide", since the low friction of Teflon allows it to slide easily. Note that claim 8 sets no restrictions on the size of the so-called slide. Cross teaches that the 96-well Teflon plate is advantageous as it is compatible with both non-polar and polar solvents, and it can be sterilized and re-used. Furthermore the 96-well format is convenient for making dilutions. However Cross does not teach methods of inducing amyloid plaques as recited in claim 1.

It would have been obvious to one of ordinary skill in the art to use a 96-well Teflon slide, as taught by Cross, in the method rendered obvious by Castillo in view of Hornbeck Grainger and Snow. The motivation to do so would be to use a format that is convenient to researchers, namely the 96-well format. Furthermore Cross teaches that the Teflon-partitioned slide is advantageous as it can be re-sterilized, thereby decreasing waste and cost. Applicant did not traverse the examiner's determination that the specific limitations of claim 8 would have been obvious in view of Cross, but argued that since the rejection of claim 1 should be withdrawn, the rejection of dependent claim 8 should be withdrawn as well. For the reasons set forth above, the invention of claim 1 is obvious, thus this rejection of claims 1 – 8 and 33 – 35 stands.

7. Claims 1 – 8, 10, and 33 – 35 are rejected under 35 U.S.C. 103(a) as being unpatentable over Castillo in view of Hornbeck, Grainger, Snow, and Cross as applied to claims 1 – 8 and 33 – 35 above, and further in view of McLaurin 1999 (Eur. J. Biochem. 266:1101-1110) and Roach (U.S. Patent 3,494,201, issued 10 February 1970, of record).

The reasons why claims 1 – 8 and 33 – 35 are obvious are set forth above. Note that Snow teaches the specific steps of staining with Congo Red and viewing under polarized light to find Maltese Cross patterns in the induced amyloid plaques. However none of the references explicitly teaches using the SGAGs recited in claim 10 to induce amyloid plaques, and none of the references explicitly teaches bubbling as recited in claim 10.

McLaurin teaches that several SGAGs, including heparin, keratan sulfate, chondoritin-6-sulfate, chondroitin-4-sulfate, and dermatan sulfate each induce formation of amyloid fibrils; see

p. 1103 first complete paragraph for example. However McLaurin does not explicitly teach immobilizing the SGAG, does not teach staining with Congo Red, and does not teach bubbling as required by claim 10.

Roach teaches pipetters which use air to displace a liquid contained within the pipetter. Roach also teaches that pressing the dispensing shaft beyond the set-point for drawing up liquid to ensure that all liquid is released (see for example column 4). The artisan of ordinary skill would have the experience to understand that when pipetting, bubbles are frequently released into the solution. This is an indication that all the solution contained within the pipet tip has left the tip and has been released into the recipient solution.

It would have been obvious to one of ordinary skill in the art to use a bubbling technique in performing the assay rendered obvious by Castillo in view of Hornbeck, Grainger, Cross, and Snow. The motivation to do so would be to ensure that all liquid from the pipet tip had been forced out; an air bubble would be a reliable indicator that this had been accomplished. Additionally, it would have been obvious to substitute any of the SGAGs taught by McLaurin for the perlecan taught by Snow and Castillo, since it is prima facie obvious to substitute equivalents known to be effective for the same purpose. Here, both perlecan and the other SGAGs (taught by McLaurin) were known to be effective in rapidly inducing formation of amyloid fibrils at the time the invention was made.

Conclusion

8. No claim is allowed.

9. Any inquiry concerning this communication or earlier communications from the examiner should be directed to DANIEL KOLKER whose telephone number is (571)272-3181. The examiner can normally be reached on Mon - Fri 8:30AM - 5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Stucker can be reached on (571) 272-0911. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Daniel E. Kolker/
Primary Examiner, Art Unit 1649
January 7, 2009